Preoperative evaluation of patients with thyroid gland disease, in any kind of surgery, should include the possibility of difficult intubation caused by thyromegaly, the hormonal status (its disbalance), as well as the screening, and therapy of consequences of thyroid imbalance on specific organ systems, especially cardiovascular. It is necessary to select the adequate anesthetics and other pharmacological agents, according to current hormonal status. It is also necessary to select the adequate medications and other therapeutic measures for prevention and treatment of possible complications in perioperative period, some of which are life-threatening (thyroid storm and mixedema coma).

Key words: preoperative care, thyroid gland, hyperthyroidism, hypothyroidism, goiter (thyromegaly)

INTRODUCTION

Thyroid hormones (TH) are the main regulators of metabolism and development. Thyroid gland synthesizes and releases triiodothyronine (T3) and thyroxine (T4). T4 is the main product of thyroid secretion, and its deiodination in peripheral tissues produces T3, the biologically active form of thyroid hormone. T3 and T4 are bound to thyroglobulin. Thyroid hormones synthesis is controlled by the thyrotropin hormone (TSH) level, which is synthesized in the anterior pituitary lobe, when TSH-releasing hormone (TRH) is present. Free T3 and T4 initiate negative feedback for the synthesis and release of TSH and TRH

These hormones play an important role in metabolism regulation: they increase basal oxygen consumption and heat generation, increase protein synthesis, accelerate cholesterol degradation, increase insulin and glucocorticoid secretion, increase glucose degradation (glycolysis), and its production (gluconeogenesis), increase cardiac output, affect the heart muscle strenght, stimulate growth and brain development in fetal period.

Hyperthyroidism is characterized by increased values of circulating TH leading to acceleration of the whole metabolism, and causing a series of signs and symptoms: tachycardia, hyperglycemia, hypercholesterolemia, restlessness and emotional instability, fever and excessive sweating, loss of weight, exophthalmos.

Hypothyroidism, due to the thyroid hormone deficiency, generally presents as a slowdown of physical and mental functions. Patients are tired, sleepy, they gain weight gradually, and eventually, if untreated, hypothyroidism can lead to mixedema and mixedema coma.

An enlarged thyroid gland, even in the absence of thyroid hormone dysfunction, has a great significance in preoperative treatment, especially from anesthesiological aspect, because of the possibility of difficult intubation.

HYPERTHYREOSIS

Thyrotoxicosis is the clinical syndrome that results as a consequence of elevated concentrations of thyroid hormones in the circulation and their toxic effect on peripheral tissues. In hyperthyreosis, thyroid gland primarily produces thyroxine T4 and in smaller scale T3 (20%).

In the preoperative evaluation and preparation of patients with thyroid gland disease for any kind of surgery it is necessary to determine serum levels of thyroid hormones T4 and T3 and the levels of the pituitary hormone TSH. When determining T4 in laboratory, it is important to emphasize that this refers to the total thyroxine, i.e. all the thyroxine fractions. Free fraction is the smaller percent of total thyroxine. Free fractions of T4 and T3 reflect the metabolic state, i.e. only they can enter the cell and bind with the thyroid receptors. Graveness of the clinical picture is in the direct proportion to the T4 values.
The recommendation is to determine both T4 and FT4, for better insight into the patient’s state.

Preoperatively diagnosed hyperthyroidism is a clinical state that demands the adequate treatment before any surgery in general endotracheal anesthesia because it has a potential to vitally endanger the patient in case of thyroid storm.

If possible, surgery should be planned only after achieving the euthyroid state of the patient using medicamental therapy. But sometimes, hyperthyroidism can be unrecognizable preoperatively, or the surgery has to be conducted immediately, thus limiting the time for preparation to only several hours or days. The way of preoperative preparation depends on the available time, the graveness of the hyperthyroidism and the effect of the current or the previous therapy.

The purpose of therapy is to put the patient in a state as close to the clinical and biochemical remission of hyperthyroidism as possible. In that way, both mortality and morbidity are extremely low.

To achieve that objective PTU, iodides and propranolol are used. Treatment with thyreosuppressive medications leads to stopping of thyroid hormones synthesis.

Reduction of the active hormones depot reservoir is achieved by the inhibition of the thyroid gland thyroxine secretion, through application of iodine in form of the Lugol’s solution, or saturated solution of potassium iodide, or in case of iodine allergy by application of Jopanoat, or Na-ipodat.

Reduction of the symptoms of hypermetabolism and elimination of tachycardia is achieved by usage of beta blockers. Propranolol is the first line medicament, because it is the only beta blocker that inhibits the peripheral conversion T4 to T3.

In case of emergency surgery, when we have 2-3 hours available, it is necessary to confirm the diagnosis by measuring FT4, FT3 as well as TSH. PTU should be applied, as the first choice drug. Simultaneously, IOP, as well as dexamethasone and propranolol are administrated parenterally, and the dosage depends on the clinical picture and drug tolerance.

Quick control of hyperthyroidism can be achieved by oral application of a radiographic contrast agent with iodide, as is iopanoic acid or ipodat, in combination with dexamethasone, antithyroid drugs and beta blockers. The confirmation of effectiveness of this approach is given in the study of Pancer and associates.

Thyrosuppressive treatment causes side effects in 3 to 12% of cases. Long-term use of thyrosuppressive drugs (methimazole) may cause leukopenia. If it comes to agranulocytosis, as the most severe form leukopenia, then all elective surgery needs to be delayed for 1 to 2 months and it is necessary to consult a hematologist and an endocrinologist in order to alter therapy.
Hearts are the most common clinical manifestations of hyperthyrosis. Sinus tachycardia is present in 40% of patients with hyperthyrosis, it is more common in younger persons, and is present in the night. Heart rate in patients with sinus tachycardia is in correlation with the graveness of the illness.

Paroxysmal supraventricular tachycardia, atrial flutter, ventricular rhythm disorders, interatrial conduction disorders can be seen in 5-15% of patients. AV blocks of second or third-degree can appear. Right bundle branch block is most usually present, in even 15% of patients.

Thromboembolic complications occur in about 15% of patients with hyperthyrosis and atrial fibrillation.

Hypertension in hyperthyrosis features an isolated increase of systolic arterial pressure, while the diastolic remains normal. Hypertension is a consequence of inability of the peripheral vascular blood flow to adapt to sudden increase of stroke and minut volume.

Reversible cardiomyopathy features increase of ejection fraction at standstill, while on treadmill it features a significant reduction. Dilated cardiomyopathy can occur in older patients with hyperthyrosis.

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Cardiac insufficiency can occur in 6% of patients with hyperthyrosis. For a long time, it was thought that cardiac insufficiency occurs in patients with existing heart disease, and that hyperthyrosis leads to its aggravation, but it is proved that the presence of thyroid hormones in excess can originate cardiac insufficiency in a previously healthy person.

Chast pains can occur in about 5% of patients with hyperthyrosis.

Pulmonary hypertension can occur in 43-65% of patients with hyperthyrosis. It manifests in right heart failure. As a possible cause for development of pulmonary hypertension in hyperthyrosis, lesion of endotel is stated, caused by increase of stroke volume, by autoimmune mechanisms, or by increase in metabolism of intrinsic pulmonary vasodilatatory substances. Normalisation of pressure in pulmonary circulation occurs with hyperthyrosis treatment.

Hyperglycemia is frequently present in patients with a long, irregular and untreated hyperthyroidism, usually in the form of diabetes mellitus type II. It is often qualified as newly discovered diabetes. If morning blood glucose levels not exceed 8 mmol/l, the operation should not be postponed, in order to evaluate diabetes.

**THYROID STORM**

Thyroid storm (TS) is an urgent condition defined as an acute, rapidly worsening of hyperthyroidism. It is a rare complication of hyperthyroidism (1-2%) with high mortality (20%) When occur in surgical patients the mortality is the highest: 10-20% in conservatively treated patients, and in the operated patients, in the perioperative period, even 30-75%. In surgical patients, thyroid storm is the most commonly consequence of unrecognized and untreated hyperthyroidism.

It usually occurs 6-24h after surgery, in patients with poorly controlled thyrotoxicity, but can also occur during surgery. TS can be diagnosed based on the following clinical manifestations: elevated TH, decreased TSH, present hyperthermia (increased body temperature over 38°C), altered mental status with agitation, tachycardia and ventricular fibrillation and heart failure. ECG shows extreme supraventricular tachycardia, and possibly atrial fibrillation. In differential diagnosis, intraoperatively, regarding the three dominant symptoms (tachycardia, hyperthermia, and hypertension) one should have in mind malignant hyperthermia, neuroleptic malignant syndrome and pheochromocytoma.

Treatment is based on the same principles as the treatment of hyperthyroidism, but the drugs are administrated parenterally. Propylthiouracil (PTU) is still the first choice drug, but for now, there is no possibility of its parenteral administration. Recent reports recommend increased single and daily dose (150mg/4-6h or 200 or 250mg/4-6 mg/h) per os, per sondam or per rectum. Methimazole (20 mg/4h IV) is an alternative drug in patients allergic to PTU.

However, Kearney recommends methimazole as first choice, because there is possibility of parenteral application. Carbimazole is used later (30mg/12h, per os). When it comes to beta adrenergic blockers, propranolol is the drug of choice (1-3 mg IV every 5-10 minutes to a maximum dose of 20mg). Esmolol can be applied in an infusion, which is particularly appropriate during surgery and in critically ill on mechanical ventilation. An alternative for treating tachycardia are calcium channel blockers and digoxin. Inorganic iodide is applied 1 hour after PTU in the form of drops (10 drops to 8 hours) or as an infusion 200 mg KJ in 500ml 0.9% NaCl at 12h or NaI 1gr/12h IV. In case of allergy to iodine can be applied to lithium carbonate (300mg/6h), with frequent checks of serum lithium concentration, due to its small therapeutic range and the possibility of overdose.

In addition, symptomatic therapy is of great importance, focused on the treating of cardiovascular, respiratory and metabolic disorders. Pure oxygen oxygenation, aggressive fluid replacement, cooling a patient, correction of acidosis etc. If atrial fibrillation is present, fast digitalisation can be done, and with atrial fibrillation refractory to digitalisation, amiodarone can be used. Also, glucocorticoids can be used because they block the conversion of T4 to T3 (Hydrocortisone 100 mg/6h or dexametazon 4mg/6h).
Use of chlorpromazine (25-100 mg/4-8h) showed to be useful because it, except sedative, has antipyretic effect (reduction in central thermogenesis)\(^3\).

The preoperative treatment is important to predict the occurrence of these, the most serious, complications of thyrotoxicosis and therapeutic measures taken to reduce the value of TH. If due to emergency surgery treatments, it is not possible, it is necessary to prepare strategies and medication to treat TS.

**HYPOTHYREOSIS**

Hypothyreosis is a clinical syndrome which originates as a consequence of thyroid hormone deficiency, with consequent general slowdown of metabolic processes in organism. Reduced thyroid hormones secretion from thyroid gland causes increased secretion of thyroid-stimulating hormone (through feedback mechanism). Subclinical hypothyreosis is a condition in which TSH concentrations are increased, while level of TH are normal. This condition can be associated with cardiovascular complications. Clinical manifestation of hypothyreosis depends on patient’s age in the moment of the manifestation of the illness and the severity of thyroid hormones deficiency\(^3\).

Concerning the operative treatment of patients with hypothyreosis, especially in nonthyroid and emergency surgery, disorders of different organs and systems, associated with hypothyreosis, should be considered.

When it comes to surgical treatment of patients with hypothyroidism as a co-morbidity, especially in emergency surgery, one think should be kept in mind, that the disturbances of various organs and organ systems, which are associated with hypothyroidism.

In terms of preoperative preparation, of particular importance are:
- cardiovascular disorders (possible myocardial depression and bradycardia)
- respiratory system disorders (reduced spontaneous ventilation)
- metabolic disorders and hydroelectrolyte and acid-base disbalance (especially hyponatremia, and hypoglycemia)\(^10\)

Due to slow metabolism in patients with hypothyroidism, there is a risk of an overdose of anesthetics and other medications that are used in the surgical treatment. It is therefore necessary to carefully titrate doses, with the general recommendation to reduce dose by 30%.

In patients with expressed hypothyreosis it is necessary to introduce substitution therapy. The optimal preparation period before the surgery is 2-4 weeks. Patients older than 60 years of age, especially with coronary disease or long term aggravated hypothyreosis, should not be given full doses of substituents in the beginning.

Bearing in mind that there is no parenteral form of drug, a specific concern is access to patients on substitutional therapy with synthetic thyroid hormones (after thyroidectomy) who will undergo surgery on the digestive tract. After digestive surgery, they will be prevented from taking medication per os for a while. The answer to this problem lies in the fact that the half-life of the thyroid hormones, both natural and synthetic, is relatively long, 3-8 days, but the drug effect is extended to 3-4 weeks. That means that the risk of hypothyroidism development is real only after the elapse of that period of time, but the recommendation is to control the hormonal status and to start the hormonal substitution via alternate ways of drug administration (rectal, per sonda), as soon as laboratory and other parameters indicate\(^11,12\).

**MIXEDEMA COMA**

Undiagnosed, unrecognized and inadequately treated hypothyroidism can progress to mixedema coma, especially in the field of an acute comorbidity, primarily infection, or surgical disease. Mixedema coma represents the most difficult, decompensated form of hypothyroidism.

Precipitating factors for the progression of hypothyroidism in mixedema coma are infectious, traumatic and vascular. In surgical patients, especially in the postoperative period, precipitating factors for hypothyroidism decompensation are: starvation, malnutrition, the use of iodine radiographic contrast agents and certain medications (amiodaron, lithium, propranolol, dexamethasone)\(^13\), and the presence of systemic diseases as a comorbidity. Mentioned precipitating factors mainly inhibit the peripheral conversion of T4 to T3, as shown by the research of Wartofsky th et al\(^14\).

In the preoperative period is very important to promptly diagnose mixedema coma. Diagnosis is based on laboratory and clinical findings. TH values are always lower. TSH values are usually high (in thyroid forms of hypothyroidism), but they can be normal, reduced or unmeasurable (in pituitary or hypothalamic hypothyroidism). Other laboratory findings are: hyponatremia, hypoglycemia, cortisol deficiency, respiratory and metabolic acidosis. The clinical and physical findings are dominated by: hypotension, bradycardia, peripheral edema, hypoventilation, hypothermia and disturbance of consciousness (from somnolence to coma). Chest radiography may show an enlarged cardiac silhouette, and pericardial and pleural effusions are frequent. ECG shows bradycardia (less commonly atrial fibrillation), prolonged QT interval, ST segment elevation, low or inverse T-wave, low voltage.

Emergency treatment includes hemodynamic monitoring, pharmacological and respiratory support. Hormone therapy is used orally, parenterally or per sonda. Intake through the digestive tract is recommended whenever possible. For parenteral use L-thyroxine (T4) or Liotironine (T3) are available. The recommended dose of L-thyroxine is 200-500µgr IV initially, and then, 50-100µgr/24 hours IV or IM, for Liotironine 10-25µgr/8 h IV, the first day to a maximum dose of 65-100µgr/24h. TH adversely affect the elderly and patients with coexisting cardiac disease, and if the patients are very old or critically ill they are not given hormones, but applies only symptomatic therapy.

Symptomatic therapy is also of great importance, which involves the correction of acidosis, hypoxia, tissue oxygenation, hypoglycemia, use an infusion of NaCl 0.9% (the upper limits of CVP) to correct hyponatremia, and if the value of the Na\(^+\) is significantly lower (110 mmol/l), it
hypertonic saline solutions can be applied. If there is a suspicion to the associated adrenal insufficiency (which is often the case in severe hypothyroidism), it is reasonable to use hydrocortisone. After obtaining an adequate response to initial therapy and initiation of metabolism, it is recommended that the patient is kept warm by external and internal sources of heat.

Adequate preoperative preparation of patients with hypothyroidism, early diagnosis and therapy of mixedema coma is of great importance for the outcome of surgical treatment of these patients. As with TS, although rare, this complication is associated with high mortality. Umpierrez et al. showed that in England, in 2004 there were 11 deaths recorded (in 500 hospitalized patients), due to mixedema coma15.

**GOITER**

Thyroid gland can be enlarged in hyperthyroidism, even in hypothyroidism, but that enlargement is small and is usually diffuse. In degenerative diseases of the thyroid gland enlargement can be enormous (up to 100 times), and is usually not diffuse, but the changes are often nodular or polynodal, while the TH function is normal. Degenerative disease of the thyroid gland is called a goiter.

The importance of goiter as a comorbidity was highest from anesthesiological aspect, because of the possibility of difficult intubation of the trachea. In these patients, screening tests for predicting difficult intubation are necessary in the preoperative preparation, as is radiography of the chest and neck. If this basic evaluation shows increased risk for securing the airway during surgery, further evaluation is recommended: CT of the neck and chest, indirect laryngoscopy etc. If this risk is confirmed, it is necessary to prepare alternative methods for securing the airway.

Enlarged thyroid gland, either external, or internal (retrosternal, mediastinal propagation) sometimes significantly dislocates the trachea or larynx (or both), or leads to tracheal stenosis, which may cause the difficulties in visualisation of upper airways and intubation (Picture 2). Our previous researches have shown that the incidence of difficult intubation is 5.5 times higher in patients with enlarged thyroid gland than in the general population16. This research has shown that male sex and hyperthyroidism are additional risk factors for difficult intubation in patients with thyroid gland disease.

When conventional methods of laryngoscopy and endotracheal intubation do not provide airway management, it is necessary to prepare the alternatives. The best choice is fiberoptic intubation. If fiberoptic bronchoscope is not available, alternative approaches for securing the airway may be applied: mask ventilation, laryngeal mask, combitube, nasotracheal intubation, rigid bronchoscope intubation, etc.

Preoperative preparation for DI includes, not only preparing additional equipment for the execution of difficult intubation, but also the preparation of medications and equipment to promptly treat any complications of difficult intubation. Complications of difficult intubation are cardiorespiratory issues, esophageal intubation, regurgitation and aspiration of gastric contents, laryngo and bronchospasm, hypoxemia, hypertension, arrhythmias, sore throat and nerve damages. It can also result in injury of various anatomical structures such as tooth, the eyes, vocal cords, tonsils and larynx, maxilla and mandible, lip, hypopharynx, esophagus, trachea and bronchi.

Retrosternal goiter may exercise a significant compression of the trachea and major blood vessels and may present as severe respiratory insufficiency or superior caval vein syndrome, which can be complicated by thrombosis, decreased cerebral perfusion (as a result of arterial compression and thyreocervical steal phenomenon), Horne’s syndrome. Therefore, all elective surgery should be postponed and retrosternal goiter should be operated first. If it comes to emergency surgery, preoperative assessment of these patients is practically inadequate, because symptomatic and palliative methods (bronchodilators and corticosteroids) can not fix airway obstruction caused by compression of the enlarged thyroid gland on the trachea and superior vena cava.

**CONCLUSION**

In patients with thyroid gland disease as a comorbidity in any kind of surgery it is necessary to evaluate hormonal and metabolic status, to prepare patients and to establish euthyreotic and eumetabolic status. When it comes to an urgent operation and life threatening conditions, which excludes an adequate preoperative preparation It is necessary to select the adequate medications and strategy for prevention and treatment of possible complications (thyroid storm and mixedema coma).

In degenerative diseases of the thyroid gland, especially those with enormous enlargement or retrosternal propagation, elective surgery should be postponed and the surgical treatment of thyroid gland should be done first. If this is not possible, due to the necessity of urgent surgical treatment, preoperative screening of difficult intubation is of most importance as are measures for prevention and treatment of complications of difficult intubation.

**SUMMARY**

**SAVREME NI KONCEPTI PREOPERATIVNE PRIPREME BOLESNIKA SA OBOLJENJEM ŠITIŠTE ŽLEZDE**

Preoperativna evalvacija bolesnika sa oboljenjem šititaste žlezde u bilo kojoj grani hirurgije trebalo bi da obuhvati mogućnost otežene intubacije, zbog tireomegalije, hormonskih stani, kao i skrining reperkusija tiroiđnog oboljenja i njegovog lečenja na pojedine organske sisteme, a naročito kardiovaskularni. Neophodan je pravilan izbor anestetika i drugih farmakoloških agenasa, u skladu sa aktuelnim hormonskim statusom. Zbog mogućnosti nastanka komplikacija u perioperativnom periodu, od kojih su neke vitalno-ugrožavajuće (tireotoksična opla i miksedeomska koma), potrebno je pripremiti medicamente i druge terapijske mere za njihovu prevenciju i lečenje.
Ključne reči: preoperativna priprema, tireoideja, hiperthireoidizam, hipotireoidizam, struma (tireomegalija)

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